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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/625,105	07/22/2003	Takashi Tsuji	14539-006002	8893

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EXAMINER	
OUSPENSKI, ILIA I	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 11/15/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/625,105	TSUJI ET AL.	
	Examiner	Art Unit	
	ILIA OUSPENSKI	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 March 2005 and 24 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *109-179* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *109-117* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/859,053.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/22/03, 5/24/04*, 3/16/05, and 5/11/05.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *3/16/2005* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. In a telephone conversation on 03/16/2005 with Applicant's Representative Jack Brennan, a Restriction Requirement and Species Election Requirement was set forth, as they applied to then-pending claims 1 – 117.

Subsequent cancellation of claims 1 – 117 and addition of new claims 118 – 179 by Applicant's amendment filed 03/24/2005 has rendered the Restriction Requirement moot.

The Species Election requirement is reiterated herein:

(A). This application contains claims directed to the following patentably distinct species of the claimed Invention, wherein the antibody comprises heavy chain which is one of:

A. a heavy chain comprising gene segment 1-02;
B. a heavy chain comprising gene segment 3-13;
C. a heavy chain comprising SEQ ID NO:28;
D. a heavy chain comprising SEQ ID NO:32;
E. a heavy chain comprising SEQ ID NO:36;

and a light chain which is one of:

F. a light chain comprising gene segment L5;
G. a light chain comprising gene segment A27;
H. a light chain comprising SEQ ID NO:30;
I. a light chain comprising SEQ ID NO:34; or
J. a light chain comprising SEQ ID NO:38.

Applicant is invited to indicate functional combinations of heavy and light chain SEQ ID NOS and gene segments readable thereon.

These species are distinct because their structures, physicochemical properties and mode of action are different, and they do not share a common structure that is disclosed to be essential for common utility. Furthermore, the examination of these species would require different searches in the scientific literature. As such, it would be burdensome to search these Species together.

Applicant is required under 35 USC 121 to elect a single disclosed species to which the claims would be restricted if no generic claim is finally held to be allowable.

(B). This application contains claims directed to the following patentably distinct species of the claimed Invention, wherein the disorder is:

A. an autoimmune disorder,
B. an allergic disorder,
C. an inflammatory disorder, or
D. graft versus host reaction, graft versus host disease, or immune rejection accompanying transplantation of a tissue or organ.

These species are distinct because the pathological conditions differ in etiologies and therapeutic endpoints; thus each condition represents patentably distinct subject matter. Furthermore, the examination of species would require different searches in the scientific literature. As such, it would be burdensome to search these Species together.

Applicant is required under 35 USC 121 to elect a single disclosed species to which the claims would be restricted if no generic claim is finally held to be allowable.

It is noted that if additional "disorders" are introduced into the claims during prosecution, they will be considered to be non-elected species. Likewise, if multiple specific diseases encompassed by the broadly defined disorders are introduced into the claims during prosecution, additional sub-species election may be required. Applicant is invited to indicate the elected sub-species at the time the specific diseases are introduced.

2. In a telephone conversation with the Examiner on 03/16/2005, Jack Brennan, Applicant's Representative, elected, without traverse, the Species of an antibody comprising a heavy chain comprising SEQ ID NO:28, encoded by gene segment 1-02, and a light chain comprising SEQ ID NO:30, encoded by gene segment L5. Applicant further elected the Species of a disorder which is an immune rejection accompanying transplantation of a tissue or an organ in a subject.

3. Applicant's amendment/remarks, filed 03/24/2005, are acknowledged.
Claims 1 – 108 have been cancelled.
Claims 109 and 113 – 117 have been amended.
Claims 118 – 179 have been added.

Claims 109 – 179 are pending.

Claims 109, 111-121, 123-126, 131, 133, 135, 137, 140, 143, 146, 149-152, 154-157, 162, 164, 166, 168, 171, 174, and 177 read on the elected Species.

However, in the interest of compact prosecution, prior art search has been extended to include all Species of antibodies, as well as all Species of disease.

Claims 109 – 179 are under consideration in the instant application.

4. An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)).

Applicant's claim for domestic priority under 35 U.S.C. 120 is acknowledged. Priority application USSN 09/859,053 appears to provide adequate support under 35 U.S.C. 112 for subject matter claimed in the instant application.

5. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d) in the priority application USSN 09/859,053, which papers are of record in the file of the priority application.

6. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention *to which the claims are directed.*

7. Applicant's IDS documents, filed 07/22/2003, 05/24/2004, 03/16/2005, and 05/11/2005 are acknowledged, and have been considered.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 109 – 179 are rejected under **35 U.S.C. 112, first paragraph**, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The following *Written Description* rejection is set forth herein.

Applicant is not in possession of monoclonal antibodies to a generically recited "human AILIM."

The specification does not appear to provide a representative description of the structural and functional properties a polypeptide must possess to fall within the scope of the instant claims, because the "AILIM" is also known in the art by a number of designations, such as ICOS, CRP1, 8F4, and JTT. Therefore, the skilled artisan cannot envision all the contemplated amino acid sequence possibilities encompassed by the instant claims.

A description of a genus of protein sequences may be achieved by means of a recitation of a representative number of polypeptide sequences, defined by amino acid sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. Regents of the University of California v. Eli Lilly&Co., 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently,

Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicant is invited to amend the claims to recite a SEQ ID NO to more specifically define the "AILIM" polypeptide.

10. Claims 109 – 114 and 118 – 148 are rejected under **35 U.S.C. 112, first paragraph**, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not provide a sufficient enabling description of the claimed invention.

The specification discloses the following activities of human monoclonal antibodies that bind to human AILIM: inhibition of mixed lymphocyte reaction in vitro (Example 8); ADCC-inducing activity in vitro (Example 9); inhibitory effect on delayed-type hypersensitivity in a monkey model (Example 11); and inhibition of proliferation of T cells associated with AILIM-mediated signaling (Example 15). This is not seen as a sufficient enabling description for a person of skill in the art to practice the claimed methods, in particular methods of treating or preventing an autoimmune disorder, an allergic disorder, an inflammatory disorder, graft versus host reaction, graft versus host disease, or immune rejection accompanying transplantation of a tissue or organ.

In vitro and animal model studies have not correlated well with in vivo clinical trial results in patients. Since the therapeutic indices of immunosuppressive drugs such as costimulation-based biopharmaceutical drugs can be species- and model-dependent, it is not clear that reliance on the experimental observations disclosed in the instant specification provides the basis for employing the claimed antibodies in the methods of treating disease. There is insufficient objective evidence that the disclosed experimental in vitro and in vivo model systems would be predictive of the therapeutic methods encompassed by the claims.

Pharmaceutical therapies in the absence of in vivo clinical data are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

With regard to inhibiting costimulatory signaling, as claimed in the instant application, Blazar et al. (J. Immunol., 1996, 157: 3250 – 3259) disclose that issues such as tissue distribution, half-life, affinity and avidity obtained with these various CD28-B7-specific reagents might prove to be highly important in achieving GVHD protection. However, any conclusion regarding the efficacy of CD28/B7 blockade on altering in vivo immune response should be interpreted in light of the type of reagent infused (Blazar see page 3257, column 2, paragraph 10). Blazar et al. further disclose that anti-CD80 or anti-CD86 antibodies were ineffective in preventing T cell CD8-mediated GVHD lethality; that each antibodies was partially effective in CD4-mediated GVHD lethality and that the combination of anti-CD80 and anti-CD86 antibodies were

effective in preventing GVHD lethality in murine experimental models (see entire document, including the Abstract).

Similarly, Perrin et al. (J. Neuroimmunol, 1996, 157: 3250 – 3259) disclose that in contrast to the effective treatment of disease with CTLA-4 Ig; anti-CD80 (B7-1) attenuated the first clinical disease episode but not the relapse, anti-CD86 (B7-2) had no significant effect on the course of disease, and the combined treatment with anti-CD80 plus anti-CD86 resulted in the exacerbation of disease (see entire document). It is also noted that CTLA-4 Ig had a marked but incomplete therapeutic effect in the EAE model.

Further, the burden of enabling the prevention of a disease (i.e. the need for additional testing) would be greater than that of enabling a treatment due to the need to screen those humans susceptible to such diseases prior to the manifestation of any symptoms, and the difficulty of proof that the administration of the drug was the agent that acted to prevent the condition. Further, the specification does not provide guidance as to how one skilled in the art would go about screening those patients susceptible to the diseases within the scope of the presently claimed invention. Nor is sufficient guidance provided as to a specific protocol to be utilized in order to prove the efficacy of the presently claimed antibodies in preventing these disease states.

In view of the lack of predictability of the art to which the invention pertains, the lack of established protocols for effective costimulation-based therapies, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive that the claimed methods are effective for treating or preventing the claimed diseases.

11. Claims 113 – 114, 116 – 117, 123 – 124, and 154 – 155 are rejected under **35 U.S.C. 112, first paragraph**, because the specification, while being enabling for methods utilizing antibodies of the specified amino acid sequences, does not reasonably provide enablement for methods utilizing antibodies "in which one to ten amino acid residues are deleted, substituted, or added." The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The specificity and affinity of the instantly claimed antibodies for the human AILIM protein are essential for practicing the claimed methods.

It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, which provide the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain variable region are critical in maintaining the binding specificity and affinity to the antigen. Even minor changes in the amino acid sequences of the heavy and light variable regions, may dramatically affect antigen-binding function as evidenced by Rudikoff et al. (Proc. Natl. Acad. Sci. USA, 1982, 79: 1979 - 1983). Rudikoff et al. teach that the alteration of a single amino acid in one CDR of a myeloma protein resulted in the loss of antigen-binding function. Furthermore, Panka et al. (Proc. Natl. Acad. Sci. USA, 1988, 85: 3080 – 3084) demonstrate that a single amino acid substitution of serine for alanine results in a decreased affinity of an antibody to its antigen.

Therefore it is unlikely that the antibodies "in which one to ten amino acid residues are deleted, substituted, or added" will have the required binding function. Thus the specification provides insufficient direction or guidance regarding how to produce antibodies as defined by the claims, which will be functional in the claimed

methods. Undue experimentation would be required to practice the claimed invention based on the written disclosure alone.

12. Conclusion: no claim is allowed.

The claims appear to be free of prior art.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILIA OUSPENSKI whose telephone number is 571-272-2920. The examiner can normally be reached on Monday-Friday 9 - 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

ILIA OUSPENSKI
Patent Examiner
Art Unit 1644

November 7, 2005

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